Current Therapies in the Management of Parkinson's Disease Psychosis

Brent Curry, Pharm.D.
PGY2 Psychiatric Pharmacy Resident
Seton Shoal Creek Hospital/
The University of Texas at Austin
College of Pharmacy
September 16th, 2016

Disclosure

• Dr. Brent Curry has no relevant conflicts of interest to disclose

Learning Objectives

After the completion of this presentation, the participant should be able to:

1. Understand the pathophysiology behind Parkinson's Disease Psychosis
2. Identify treatment options for the management of Parkinson's Disease Psychosis
3. Summarize the research on the newest available agent for the treatment of Parkinson's Disease Psychosis
Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIMS</td>
<td>Abnormal Involuntary Movement Scale</td>
</tr>
<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
</tr>
<tr>
<td>CGI-S</td>
<td>Clinical Global Impression Scale</td>
</tr>
<tr>
<td>COMT</td>
<td>Catechol-O-methyl transferase</td>
</tr>
<tr>
<td>MAO-B</td>
<td>Monoamine oxidase B</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-Mental Status Exam</td>
</tr>
<tr>
<td>NINDS</td>
<td>National Institute of Neurological Disorders and Stroke</td>
</tr>
<tr>
<td>NPI</td>
<td>Neuropsychiatric Inventory</td>
</tr>
<tr>
<td>PANSS</td>
<td>Positive and Negative Syndrome Scale</td>
</tr>
<tr>
<td>PDP</td>
<td>Parkinson’s Disease Psychosis</td>
</tr>
<tr>
<td>SAPS</td>
<td>Scale for the Assessment of Positive Symptoms</td>
</tr>
<tr>
<td>UPDRS</td>
<td>Unified Parkinson’s Disease Rating Scale</td>
</tr>
</tbody>
</table>

Parkinson’s Disease Psychosis

What is PDP?

- Part of spectrum of neuropsychiatric disorders in Parkinson’s disease patients
- NINDS/NIMH Criteria for PDP:
  - Primary diagnosis of Parkinson’s disease
  - Symptoms occur after onset of Parkinson’s
  - Presence of at least one psychotic symptom
  - Recurrent or continuous for one month
- Associated with:
  - Patient morbidity
  - Caregiver burden
  - Early mortality

References:
Prevalence of PDP
- Prevalence varies widely → from 16% up to 75%
  - Recent study reported prevalence as 60% in 116 Parkinson’s disease patients in outpatient clinic setting
  - Similar study in 250 community-based Parkinson’s disease patients reported prevalence as 26%
  - In all studies, visual hallucinations are the most common psychotic symptom
  - Auditory hallucinations are less common and delusions even less common

Psychotic Symptoms
- Consist of:
  - Illusions
  - False sense of presence
  - Hallucinations (visual and auditory)
  - Delusions
  - Insight usually retained initially
  - The phenomenology of psychotic symptoms unique to Parkinson’s disease → suggest disease-specific vs. drug-induced etiology

Pathophysiology
- Dopaminergic system considered to play pivotal role in pathophysiology
- Link with medications is inconsistent
- Complex interplay

Risk Factors (Exogenous and endogenous)
Signaling pathways (multiple neurotransmitters)
Pathophysiology

- Neuropathology
- Neuroimaging
- Neurotransmitters
- Neuro-signaling pathways

Treatment Options for Parkinson’s Disease Psychosis

- Rule out other causes of psychosis
- Relationship between symptoms and medications difficult to interpret and separate
- Limit use of dopaminergic medications \( \rightarrow \) symptoms may persist after medications stopped or reduced
- Ensure that motor function is maintained
  - Continue carbidopa/levodopa and readjust

Treatment Considerations

Chang A, Fox SH. Psychosis in Parkinson’s Disease. Drugs 2016; 76:193-1118

Review of Medications

- Limit use of non-essential non-Parkinson’s disease medications:
  - Tricyclic antidepressants
  - Bladder antispasmodics
  - Benzodiazepines
  - Muscle relaxants
  - Opioids

- Consider tapering and eliminating:
  - Anticholinergics
  - MAO-B inhibitors
  - Amantadine
  - Dopamine Agonists
  - COMT inhibitors

Guideline Recommendations

- Clozapine should be considered for patients with Parkinson’s disease and psychosis (Level B)
  - Associated with agranulocytosis and absolute neutrophil count must be monitored
- Olanzapine should not be routinely considered for patients with Parkinson’s disease and psychosis (Level B)
- Quetiapine may be considered for patients with Parkinson’s disease and psychosis (Level C)

Other Recommendations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Practice Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Efficacious</td>
<td>Acceptable risk w/ specialized monitoring</td>
<td>Clinically useful</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Unlikely efficacious</td>
<td>Unacceptable risk</td>
<td>Not useful</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Insufficient evidence</td>
<td>Acceptable risk w/o specialized monitoring</td>
<td>Investigational</td>
</tr>
</tbody>
</table>

Chang A, Fox SH. Psychosis in Parkinson’s Disease. Drugs 2016; 76:193-1118

Unified Parkinson’s Disease Rating Scale (UPDRS)

| Part I | Evaluation of mentation, behavior, and mood |
| Part II | Self-evaluation of the activities of daily life (ADLs) including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food |
| Part III | Clinician-scored monitored motor evaluation |
| Part IV | Complications of therapy |
| Part V | Hoehn and Yahr staging of severity of Parkinson’s disease |
| Part VI | Schwab and England ADL scale |

Ratings Scales

<table>
<thead>
<tr>
<th>Scale</th>
<th>Measure</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Psychiatric Rating Scale</td>
<td>BPRS</td>
<td>Measures psychiatric symptoms</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory</td>
<td>NPI</td>
<td>Assesses neuropsychiatric symptoms of those with Alzheimer’s</td>
</tr>
<tr>
<td>Positive and Negative Syndrome Scale</td>
<td>PANSS</td>
<td>Measures symptom severity of schizophrenia</td>
</tr>
<tr>
<td>Scale for Assessment of Positive Symptoms</td>
<td>SAPS</td>
<td>Measures positive symptoms in schizophrenia</td>
</tr>
</tbody>
</table>

Clozapine Pollak et al. (2004)

**Design**
- 4-week, randomized, double-blind, parallel-group comparison of clozapine and placebo
- Followed by 12-week clozapine open phase and then 1-month washout period in 60 patients
- Clozapine titrated from 6.25 mg/day and increased a maximum of three 12.5 mg steps each week up to a maximum of 50 mg/day

**Outcomes**
- Primary efficacy outcome was CGI-S
- The positive subscore of PANSS used as secondary efficacy parameter
- UPDRS and MMSE as safety outcomes

Clozapine
Pollak et al. (2004)

Results
• Mean dose of clozapine was ~36 mg/day at end of double blind period
• Mean scores on CGI-S improved by 1.8 for clozapine group compared with 0.6 for placebo group (P = 0.001)
• Mean positive subscore of PANSS improved by 5.6 for clozapine group and 0.8 for placebo group (P < 0.0001)

Limits
• 19/25 (76%) experienced a relapse within one month of washout period
• The UPDRS motor and MMSE mean scores did not change significantly in either group

Clozapine vs. Quetiapine
Morgante et al. (2004)

Design
• 12-week randomized, rater-blinded trial
• 40 patients with PDP treated with either clozapine (n=20) or quetiapine (n=20)
• Clozapine started at 6.25 mg/day and titrated up to 50 mg/day
• Quetiapine started at 25 mg/day and titrated up to 200 mg/day

Outcomes
• Severity of psychosis assessed using:
  • BPRS total, BPRS 5-items, and CGI-S
• Motor impairment assessed using UPDRS-III and dyskinesias assessed using AIMS

Demographic and Clinical Features of the Patients Completing the Study

<table>
<thead>
<tr>
<th>Features</th>
<th>Quetiapine (n=20)</th>
<th>Clozapine (n=20)</th>
<th>Differences Between Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRS total</td>
<td>Baseline</td>
<td>37.1 ± 6.1</td>
<td>37.4 ± 5.4</td>
</tr>
<tr>
<td></td>
<td>Endpoint</td>
<td>38.7 ± 4.2</td>
<td>26.7 ± 3.6</td>
</tr>
<tr>
<td>BPRS (5 items)</td>
<td>Baseline</td>
<td>15.5 ± 3.4</td>
<td>16.4 ± 2.6</td>
</tr>
<tr>
<td></td>
<td>Endpoint</td>
<td>8.4 ± 1.5</td>
<td>8.5 ± 2.0</td>
</tr>
<tr>
<td>CGI-S</td>
<td>Baseline</td>
<td>3.6 ± 0.7</td>
<td>3.8 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>Endpoint</td>
<td>2.2 ± 0.6</td>
<td>1.9 ± 0.6</td>
</tr>
<tr>
<td>UPDRS-III</td>
<td>Baseline</td>
<td>53 ± 11</td>
<td>56 ± 9.4</td>
</tr>
<tr>
<td></td>
<td>Endpoint</td>
<td>54 ± 11</td>
<td>56.7 ± 9.2</td>
</tr>
<tr>
<td>AIMS</td>
<td>Baseline</td>
<td>7.8 ± 2</td>
<td>7.2 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>Endpoint</td>
<td>6 ± 1.3</td>
<td>5.4 ± 1.3</td>
</tr>
</tbody>
</table>
Clozapine vs. Quetiapine
Morgante et al. (2004)

**Results**
- Mean dosages of 91 mg/day in quetiapine arm and 26 mg/day in clozapine arm
- Psychosis scores improved significantly in both groups as recorded on both BPRS and CGI-S ($P < .001$)
- UPDRS-III scores remained stable in both groups
- Statistically significant decrease in dyskinesia ($P < 0.05$) in both groups

**Limits**
- Motor worsening was reported in 3 patients on quetiapine
- 5/40 (12.5%) patients dropped out due to adverse effects
- 3 patients in clozapine arm, 2 patients in quetiapine arm

---

Clozapine vs. Quetiapine
Merims et al. (2006)

**Design**
- 22-week parallel-group, randomized controlled trial comparing quetiapine ($n = 13$) and clozapine ($n = 14$)
- Dose adjustments gradually increased every 2 weeks during the first 10 weeks (maximal 50 mg/day for clozapine and 150 mg/day for quetiapine) until psychosis considered under “satisfactory control”

**Outcomes**
- Primary endpoints were selected items (hallucinations and delusions) from NPI and CGI-C questionnaires
- Assessments done by a blinded neuropsychologist
- Motor worsening assessed using UPDRS

---

The CGIC (mean scores) from baseline scores over time in the 2 treatment groups
Hallucinations and delusions frequency (mean NPI scores) over time in both treatment groups

Clozapine vs. Quetiapine
Merims et al. (2006)

**Results**
- 11 patients (~80%) from each arm reached “satisfactory control”
- Mean dose was 91 mg/day for quetiapine and 13 mg/day for clozapine
- No worsening in motor symptoms as measured by UPDRS in either treatment arm

**Limits**
- Only 7/14 patients randomized to receive clozapine and 9/13 randomized to receive quetiapine completed the study
- One patient developed severe neutropenia with clozapine and 2 others discounted due to decreases in leukocytes

Quetiapine

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Results</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondo et al. (2005)</td>
<td>Double-blind, placebo-controlled, parallel group study</td>
<td>Patients randomized in a 2:1 ratio to 12 weeks of treatment with quetiapine (n = 10)</td>
<td>None of the hallucinations, psychosis, or motor impairment assessments changed significantly on quetiapine</td>
<td>4/17 (24%) patients on quetiapine that completed study reported subjective worsening</td>
</tr>
<tr>
<td>Rabey et al. (2007)</td>
<td>Double-blind, placebo-controlled, parallel group</td>
<td>12-week trial investigating total of 58 patients (quetiapine n = 30, mean dosage 139.2 ± 56.4 mg/day; placebo n = 28)</td>
<td>Compared to placebo none of BPRS or CGI-S scores changed significantly on quetiapine</td>
<td>High dropout rate of 45% (n = 26) primarily due to lack of efficacy</td>
</tr>
</tbody>
</table>
Olanzapine

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Results</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breier et al.</td>
<td>placebo-controlled, double-blind, parallel-group randomized controlled trials</td>
<td>Patients randomized 1:1 in the U.S. study (n=83), and 2:1 in the European study (n=177) to receive olanzapine (mean dosage 4.2 mg ± 2.6 and 4.1 mg ± 2.0, respectively) or placebo</td>
<td>No significant treatment group differences in any psychosis ratings on BPRS were found in either study</td>
<td>Motor function worsened significantly in patients on olanzapine compared to placebo as measured by UPDRS</td>
</tr>
<tr>
<td>Ondo et al.</td>
<td>Double-blind, placebo-controlled, parallel-group, randomized controlled trial</td>
<td>30 patients with PDP underwent 9 weeks of treatment with olanzapine (mean dosage 4.6 mg/day) or placebo (2:1 ratio)</td>
<td>Failed to detect significant differences between olanzapine and placebo in any of psychosis measures</td>
<td>Significant worsening of UPDRS motor scores in the olanzapine arm</td>
</tr>
</tbody>
</table>

Other Atypical Antipsychotics

- Open-label trial involving 14 patients with PDP treated with aripiprazole
  - 6/14 (43%) patients experienced improvement in psychosis
  - 8/14 (57%) patients discontinued treatment due adverse effects
- 4-week, randomized, single-blind, open-label, parallel comparison of ziprasidone and clozapine in 16 patients with PDP
  - 14/16 patients completed the study ➞ 8 patients on clozapine and 6 patients on ziprasidone
  - Ziprasidone seemed to be at least as effective as clozapine as psychotic symptoms reduced in both groups
Mechanism of Action

- Acts as an inverse agonist and antagonist
- High affinity for 5-HT_{2A} receptors and low affinity for 5-HT_{2C} receptors
- No affinity for 5-HT_{2B}, dopaminergic (including D_{2}), muscarinic, histaminergic, or adrenergic receptors

Pharmacokinetics

- Distribution: $V_d$: 2,173 L
- Protein binding: ~95%
- Metabolism: Primarily via CYP3A4 and CYP3A5; forms active N-desmethylated metabolite
- Elimination half-life:
  - Pimavanserin: ~57 hours
  - N-desmethylated metabolite: ~200 hours
- Time to peak: 6 hours (median: 4 to 24 hours)
- Excretion: Feces (<2%); urine (<1% as unchanged)

Dose: 34 mg/day taken with or without food

- Dose adjustment needed with concomitant therapy of strong CYP3A4 inhibitors/inducers
- Not recommended in severe renal/hepatic impairment

AEs: CNS depression, orthostatic hypotension, QTc-prolongation, peripheral edema, confusion, hallucinations, abnormal gait, nausea, constipation
Studies Evaluating Pimavanserin

Meltzer et al. (2010) – Phase II study

**Design**
- Double-blind, randomized multi-center 28-day study
- Tolerability and efficacy of pimavanserin (doses up to 60 mg/day) compared to placebo in 60 patients with PDP

**Outcomes**
- Antipsychotic efficacy evaluated using SAPS
- SAPS total domain score was chosen as principal outcome measure for efficacy
- Motor function evaluated using UPDRS

Meltzer et al. (2010):
Mean (SD) Baseline and Day 28 SAPS Scores Change from Baseline (Screening Visit) to Day 28

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pimavanserin (n=24)</th>
<th>Placebo (n=28)</th>
<th>LS mean difference</th>
<th>95% CI</th>
<th>P value</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>16.7 (7.45)</td>
<td>11.0 (11.09)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 28</td>
<td>11.0 (11.79)</td>
<td>16.8 (14.35)</td>
<td>−4.6</td>
<td>−10.0</td>
<td>0.09</td>
<td>0.56</td>
</tr>
<tr>
<td>SAPS total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(H+D) domain score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Meltzer et al. (2010) – Phase II study

Results
• Pimavanserin did not differentiate from placebo with regard to motor impairment, sedation, hypotension, or other side effects

Limits
• Principal measures of efficacy of antipsychotic response, the SAPS total domain score, only showed a trend

Cummings et al. (2014) – Phase III study

Design
• 6 week, randomized, double-blind, placebo-controlled
• After 2 week non-pharmacological lead-in phase, patients randomly allocated (1:1) to receive pimavanserin 40 mg/day (n=90) or placebo (n=95)

Outcomes
• Antipsychotic benefit evaluated using SAPS-PD
• Safety and tolerability in all patients

Results
• Pimavanserin was associated with a -5.79 decrease in SAPS-PD scores compared with -2.73 for placebo (difference -3.06, 95% CI -4.91 to -1.20; P = 0.001)
• Pimavanserin was well tolerated with no significant safety concerns or worsening of motor function

Limits
• 10 patients in the pimavanserin group discontinued because of an adverse event
• 4 patients experiencing hallucinations within 10 days of start of pimavanserin
Yasue et al. (2015)

**Design**
- Meta-analysis of randomized placebo-controlled trials
- Included 417 drug-treated and 263 placebo-treated PDP patients over 4 trials (2 unpublished trials)

**Outcomes**
- Comparison of SAPS-H+D scores (primary)
- Comparison of SAPS-H, SAPS-D, UPDRS-II+III scores, discontinuation rates, and individual adverse events (secondary)

**Results**
- Pimavanserin significantly decreased SAPS-H+D scores compared to placebo (difference -2.26, 95% CI -3.86 to -0.67; P=0.005)
- Pimavanserin was superior to placebo for reducing SAPS-H and SAPS-D scores
- Pimavanserin was associated with less orthostatic hypotension than placebo
- There were no significant differences in rates of all-cause discontinuation, adverse events, death, UPDRS scores, and incidences of individual adverse events

**Antipsychotic Medication**

<table>
<thead>
<tr>
<th>Antipsychotic Medication</th>
<th>Decrease in Psychotic Symptoms</th>
<th>Lack of Motor Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+ / -</td>
<td>+ / -</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pimavanserin</td>
<td>+ / -</td>
<td>+</td>
</tr>
</tbody>
</table>

* = Positive outcomes in trials  +/- = Mixed outcomes in trials  -- = Negative outcomes in trials
Treatment Considerations with Pimavanserin

- Cost → 17 mg (60): AWP = $2,340
- Currently only available through restricted access program and limited wholesalers
- Significant drug-drug interactions with CYP 3A4 inducers and inhibitors
- Avoid use in those with QT prolongation or on other drugs that can prolong QT interval
- Concerns about safety including the rates for severe adverse effects and deaths
- Post hoc analysis of open-label extension study showed significant increase in mortality of those taking concurrent antipsychotics (IRR 4.20, 95% CI 2.13-7.96)

Place in Therapy for Pimavanserin

- No other FDA-approved drugs for PDP
- Other treatment options have several limitations and concerns for safety and adverse effects
- Unique mechanism of action opens door for further research
- Potential to be first choice treatment option for PDP

Management of PDP

- Rule out other causes of psychosis
- Limit use of dopaminergic agents
- Quetiapine (low-dose)
- Pimavanserin (34 mg daily)
- Clozapine (low-dose)
Patient Case

In the geriatric clinic where you are the clinical pharmacist, a provider approaches you asking for a recommendation for one of his patients after a recent visit. The patient is a 70-year-old man with a 10-year history of Parkinson's disease being treated with carbidopa/levodopa (25/250-mg tablets PO Q4H) and pramipexole (1.5 mg PO Q8H). He had not been experiencing motor fluctuations. But during the visit, the patient remarked that “the leprechauns had been coming out more than usual in the few last weeks.” The patient’s family explained that he had been seeing small people dressed in costumes sitting in his living room over the last few months. The patient thought “the leprechauns” were amusing and did not report being bothered by these hallucinations.


Acknowledgements

- Dr. Brent Curry would like to thank the following people for their assistance in preparation of this presentation:
  - Lisa Mican, Pharm.D., BCPP
  - Kattura, Rania, Pharm.D., MsPhr, BCPP
  - Melissa Lewis, Pharm.D., BCPP
  - Kasey Leggette Peña, Pharm.D.
  - Stephen Saklad, Pharm.D., BCPP